

REMARKS

No claims have been canceled, amended or added in this paper. Therefore, claims 2-10 and 34-48 are pending and are under active consideration.

Claims 2-6 and 34-48 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Chesi (US 5,017,607) in view of Kushner et al., (Canadian Journal of Physiology and Pharmacology (1999), 77(2), 79-88)." In support of the rejection, the Patent Office states the following:

Scope of prior art

Chiesi teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the methyl ester of levodopa combined with other active ingredients including carboxylase and monoaminoxidase inhibitors (abstract). As such the teaching of Chiesi is taken to teach both levodopa methyl ester, pharmaceutical compositions comprising levodopa and method treating Parkinson's.

Ascertaining the difference between prior art and instant claims

Although levodopa methyl ester of Chiesi comprises deuterium at its natural abundance, Chiesi fails to teach deuterated ester of levodopa as recited in the instant claims.

Secondary reference

Kushner discloses that it is advantageous to deuterate pharmaceutical compounds because isotopic enhancement of known drugs leads to enhancement of efficacy of known pharmaceuticals by improving the activity and increased duration of actions compared to the non-deuterated (non-isotopically enhanced) known drugs. Kushner describes that the deuterated forms of drugs often have different actions than the protonated forms. Some deuterated drugs show different transport processes. Most are more resistant to metabolic changes, especially those changes mediated by cytochrome P 450 systems. Deuteration may also change the pathway of drug metabolism (metabolic switching). Changed metabolism may lead to increased duration of action and lower toxicity. It may also lead to lower activity, if the drug is normally changed to the active form *in*

vivo. Deuteration can also lower the genotoxicity of therapeutic compounds. Deuteration increases effectiveness of compounds by preventing their breakdown by target microorganisms. See page 83+.

Obviousness

The issue at hand is whether one skilled in the art at the time the instant invention was made would have found it obvious to prepare deuterated version of the methyl ester of levodopa and to utilize it in treatment of Parkinson's disease.

One skilled in the art would have found it obvious to prepare the deuterated versions of the methyl ester of levodopa. Levodopa is a well known drug that is widely utilized for treatment of neurological diseases including Parkinson's and restless leg syndrome. There is inherent motivation to improve on the bioavailability, activity and efficacy of the LDOPA and its prodrugs (methyl ester is a prodrug or LDOPA). Kushner teaches that such improvements can be attained by preparing deuterated versions of the known drugs.

In this regard, based on Kushner, those of ordinary skill would have been motivated to prepare those deuterated species that are instantly claimed, since these compounds would predictably have enhanced efficacy, activity, bioavailability and duration of action. Therefore, the instant claimed deuterated compounds are *prima facie* obvious. Pharmaceutical compositions and the method of using the instant compounds are also obvious. One skilled in the art would find it obvious to use the deuterated variant of LDOPA prodrug to perform the same treatment as is already practiced with protonated variant.

Applicant respectfully traverses the subject rejection. As best understood by Applicant, the Patent Office appears to be taking the position (i) that Chiesi teaches the claimed compound and the claimed method, except for the claimed deuteration; (ii) that Kushner et al. teaches deuterated pharmaceutical compounds; and (iii) that it would have been obvious to deuterate the Chiesi compound since Kushner et al. allegedly teaches the "enhanced efficacy, activity, bioavailability and

duration of action” of deuterated compounds. Applicant respectfully disagrees with the Patent Office’s line of reasoning for at least the reasons below.

It is well-settled that a proposed modification is proper only when there is a reasonable expectation that the modification will be successful. Applicant respectfully submits that such a reasonable expectation of success is lacking in the present case. Kushner et al. does not provide a basis from which a person of ordinary skill in the art could have reasonably expected that deuterating the particular compound of Chiesi would have the result desired. Instead, all that Kushner et al. does is merely speculate about the action that a deuterated compound **may possibly** have. In fact, if anything, Kushner et al. suggests that deuteration **does not typically lead to a predictable result**. To wit, Applicant notes that Kushner et al. states in its Abstract that “[t]he deuterated forms of drugs **often** have different actions than the protonated forms. **Some** deuterated drugs show different transport processes.” (Emphasis added.)

The Patent Office appears to be arguing that Kushner et al. teaches, in general, that it is advantageous to deuterate pharmaceutical compounds and that doing so increases the activity of the compounds. Applicant respectfully disagrees with the Patent Office’s reading of Kushner et al. At best, all that Kushner et al. teaches is that every deuteration has to be investigated in order to determine its effect. Therefore, it is necessary to test every single compound to find out if the compound is modified in its action as compared to the protonated form.

Consequently, a person of ordinary skill in the art, after having read Kushner et al., would have had no way of reasonably expecting that deuteration of the Chiesi compound would have the effect now being claimed by the Patent Office.

Moreover, Applicant notes that Dewar et al., which was previously relied upon by the Patent Office, supports Applicant's position. Dewar et al. investigated the racemic DL-DOPA and found that deuterium substitution does not affect catecholamine deamination or beta-hydroxylation in vivo. As shown in Fig. 1 of Dewar et al., there is no statistical difference between treatment with DL-Dopa and D3-DL-Dopa (see Dewar et al. at page 679, conclusion). Consequently, Dewar et al. gives no hint to a person of ordinary skill in the art that deuteration of catecholamine would lead to improved pharmacokinetic and/or pharmacodynamic properties. A principal difference between Dewar et al. and the present invention is that Dewar et al. uses racemic deuterated DL-Dopa and not deuterated L-Dopa as the pure single L-enantiomer. The use of the deuterated L-enantiomer leads surprisingly to significantly improved pharmacokinetic and/or pharmacodynamic properties. These surprisingly improved properties have been discussed in previous responses. Furthermore, there is enclosed herewith another example of an experiment that shows that the substitution of DOPA with deuterium at different positions leads to unpredictable results. (If necessary, Applicant will submit this information in the form of a declaration.)

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 2-5, 7-10 and 34-48 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Milman et al (US 5,525,631) in view of Kushner et al., (Canadian Journal of Physiology and Pharmacology (1999), 77(2), 79-88)." In support of the rejection, the Patent Office states the following:

Scope of prior art

Milman teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the ethyl ester of levodopa combined with other active ingredients

including carboxylase and monoaminoxidase inhibitors (abstract, col. 3, lines 48-55). As such the teaching of Milman is taken to teach both levodopa ethyl ester, pharmaceutical compositions comprising levodopa and method treating Parkinson's.

Ascertaining the difference between prior art and instant claims

Although levodopa ethyl ester of Milman comprises deuterium at its natural abundance, Milman fails to teach deuterated ester of levodopa as recited in the instant claims.

Secondary reference

Kushner discloses that it is advantageous to deuterate pharmaceutical compounds because isotopic enhancement of known drugs leads to enhancement of efficacy of known pharmaceuticals by improving the activity and increased duration of actions compared to the non-deuterated (non-isotopically enhanced) known drugs. Kushner describes that the deuterated forms of drugs often have different actions than the protonated forms. Some deuterated drugs show different transport processes. Most are more resistant to metabolic changes, especially those changes mediated by cytochrome P 450 systems. Deuteration may also change the pathway of drug metabolism (metabolic switching). Changed metabolism may lead to increased duration of action and lower toxicity. It may also lead to lower activity, if the drug is normally changed to the active form *in vivo*. Deuteration can also lower the genotoxicity of therapeutic compounds. Deuteration increases effectiveness of compounds by preventing their breakdown by target microorganisms. See page 83+.

Obviousness

The issue at hand is whether one skilled in the art at the time the instant invention was made would have found it obvious to prepare deuterated version of the ethyl ester of levodopa and to utilize it in treatment of Parkinson's disease.

One skilled in the art would have found it obvious to prepare the deuterated versions of the ethyl ester of levodopa. Levodopa is a well known drug that is widely utilized for treatment of neurological diseases including Parkinson's and restless leg syndrome. There is inherent motivation to improve on the bioavailability, activity and efficacy of the LDOPA and its prodrugs (ethyl ester is a known

prodrug or LDOPA). Kushner teaches that such improvements can be attained by preparing deuterated versions of the known drugs.

In this regard, based on Kushner, those of ordinary skill would have been motivated to prepare those deuterated species that are instantly claimed, since these compounds would predictably have enhanced efficacy, activity, bioavailability and duration of action. Therefore, the instant claimed deuterated compounds are prima facie obvious. Pharmaceutical compositions and the method of using the instant compounds are also obvious. One skilled in the art would find it obvious to use the deuterated variant of LDOPA prodrug to perform the same treatment as is already practiced with protonated variant.

Applicant respectfully traverses the subject rejection for analogous reasons to those discussed above in connection with the previous rejection.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

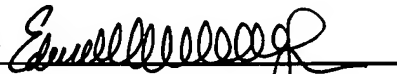
In conclusion, it is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

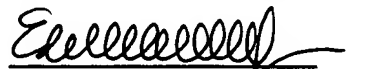
Respectfully submitted,

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Dated: *March 2, 2010*

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on *March 2, 2010*.


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Example

Striatal dopamine output measured by microdialysis

The striatal output of dopamine was measured in Male Wistar rats following intraperitoneal administration of 50 mg/kg of L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha-deutero-L-DOPA), L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (beta-beta-dideutero-L-DOPA) and L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid, compared to 50 mg/kg of L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA). Male wistar rats (BK Universal, Sollentuna, Sweden) weighing about 300 g at the time of experiment were anaesthetized with a cocktail containing fentanyl citrate (0.39 mg/kg) and fluanisone (12.5 mg/kg, Hypnorm®, Janssen-Cilag) and midazolam (6.25 mg/kg, Dormicum®, Roche) diluted in distilled water (1:1:2; 5 ml/kg i.p.) and mounted in a stereotaxic frame. Dialysis probes were implanted in the dorsolateral striatum (AP: +0.6; ML + 3.0; DV -6.2 relative to bregma and the dural surface according to the atlas of Paxinos and Watson (1998)). Dialysis occurs through a semipermeable membrane (Filtral AN69, Hospal Industrie, France) with an active surface length of 3.5 mm. Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. The rats received 30 min before administration of test items 10 mg/kg Carbidopa, (i.p.). The dialysis probe was perfused with a physiological perfusion solution (Apoteksbolaget, Sweden) at a rate of 2.5ml/min set by a microinfusion pump (Harvard Apparatus, Holliston, MA). Dialysate was collected over 15 min intervals and automatically injected into a high performance liquid chromatography (HPLC) system. On-line quantification of dopamine in the dialysate was accomplished by electrochemical detection (ESA, Chelmsford, MA). The location of microdialysis probes was verified in slices of formalin-fixed tissue stained with neutral red. The baseline corrected concentrations (fmol/min) were plotted over the time.

Comparison of AUC_{0-t} (area under the curve) values revealed that the increase of dopamine in the striatum following administration of 50 mg/kg of L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha-deutero-L-DOPA) and of L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (beta-beta-dideutero-L-DOPA) was about 25% less than after the same dose L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA) (Table 1). This is in contrast to the finding that the striatal dopamine output was significantly higher after 50 mg/kg of L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid (alpha,beta,beta-trideutero-L-DOPA) as compared to L-DOPA (Table 1). Therefore, it was not predictable from the number and position of deuterium, whether a selectively deuterated L-DOPA derivative caused decreased or increased striatal dopamine levels.

Table 1 Median AUC of the baseline corrected dopamine output in the striatum

Compound	AUC [% AUC _{L-DOPA}]
L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA)	100.00
L-2-Amino-2-deutero-3-(3,4-dihydroxyphenyl) propionic acid	75.92
L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid	234.00
L-2-Amino-3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid	75.77